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APPLICATION NO.	FILING DATE	FIRST-NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/727,355	12/03/2003	Ih-Jen Su	12563-020001	5446

69713 7590 09/26/2007
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EXAMINER	
SHIN, DANA H	

ART UNIT	PAPER NUMBER
1635	

MAIL DATE	DELIVERY MODE
09/26/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/727,355	SU ET AL.	
	Examiner	Art Unit	
	Dana Shin	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 August 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-30,32-35,37-40 and 42* is/are pending in the application.

4a) Of the above claim(s) *1-26,30,35,40 and 42* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *27-29,32-34 and 37-39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on August 20, 2007 has been entered.

Status of Claims

Claims 1-30, 32-35, 37-40, and 42 are pending in the instant application. Claims 1-26, 30, 35, 40, and 42 have previously been withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to nonelected inventions, there being no allowable generic or linking claim. Accordingly, claims 27-29, 32-34, and 37-39 are currently under examination on the merits in the instant case.

Response to Amendment

The declaration filed on July 18, 2007 under 37 CFR 1.131 is now considered and is deemed sufficient to overcome the Morrissey et al. reference (US 2003/0206887 A1).

Response to Arguments

Applicant's arguments with respect to claims 27-29, 32-34, and 37-39 have been considered but are moot in view of the new ground(s) of rejection. See below.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 27-29, 32-34, and 37-39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kay et al. (US 2003/0139363 A1, applicant's citation) in view of Stuyver et al. (US 6,709,812 B1), Goodarzi et al. (*Journal of General Virology,* 1990, 71:3021-3025), and Welch et al. (*Gene Therapy,* 1997, 4:736-743).

The claims are drawn to methods of reducing HBV expression and inhibiting viral replication in a cell comprising introducing a DNA vector containing RNA duplex structure comprising SEQ ID NO:3, which is targeted to HBsAg of HBV gene.

Kay et al. teach a method of reducing HBV expression and HBV viral replication in mammalian cells *in vitro* and in mice *in vivo* by introducing an expression vector comprising an shRNA targeted to HBV RNA sequence, wherein the expression vector reduces HBsAg expression level and inhibits HBV viral replication in cells as well as in mice. See paragraphs 0011, 0240-0243, 0245-0247. In their examples, they measure and compare the expression level of HBsAg between the experimental cells treated with shRNAs targeted to HBV and control cells treated with control shRNAs and verify whether HBV viral expression/replication is inhibited or reduced in the experimental cells. See paragraphs 0231-0243. They teach that the RNAi target sequences in their study are chosen based on the sequence conservation among the major HBV genotypes, wherein 4 out of 7 shRNAs are targeted to the HBV S-antigen. See paragraph 0240. They further teach that a specific target region for antisense oligonucleotide can be selected by an empirical method, wherein several candidate sequences are assayed for their ability to inhibit target gene expression in an *in vitro* or *in vivo* animal model. See paragraph 0119. Kay et al. do not teach that the shRNA vector comprises SEQ ID NO:3 of the instant application.

Stuyver et al. teach a sense amplification and sequencing primer for HBV, which is named "HBPr75 (or SEQ ID NO:75)" and hybridizes to the HBsAg region of HBV. See Table 1. The primer sequence of Stuyver et al. comprises the entire 19 nucleotides of the instantly

claimed HBV siRNA sequence of SEQ ID NO:3. See below for nucleotide sequence alignment between the instant SEQ ID NO:3 ("Qy") and SEQ ID NO:75 of Stuyver et al. ("Db").

```
Qy          1 GGTATGTTGCCCGTTTGTC 19
              ||||||||||||||||||||
Db          4 GGTATGTTGCCCGTTTGTC 22
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Stuyver et al. teach that the primer comprising SEQ ID NO:75 amplifies the HBsAg region in a PCR amplification. See column 23. They teach, "Protection against HBV infection of all subtypes is conferred by antibodies to the common 'a' determinant of the HB surface antigen (HBsAg)." See column 2, lines 2-4. They teach that the most important region of antigenicity is located between amino acids 124 and 147, which therefore embraces all 19 nucleotides of SEQ ID NO:3 claimed in the instant case. See column 2, line 7 and Figure 1D. Moreover, as Figure 1D illustrates (replicated below), the 19 nucleotides of SEQ ID NO:3 claimed in the instant case are faithfully shared by 35 different HBV genomic sequences, except that there are one or two nucleotide substitutions in three HBV genomic sequences.

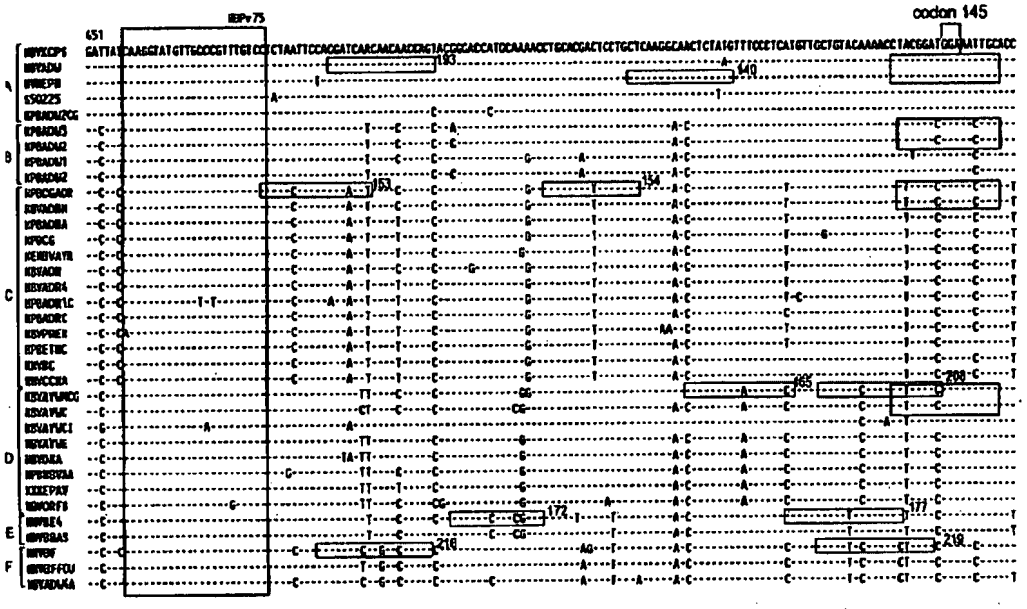

Fig.1D

Goodarzi et al. teach that 15-mer antisense oligonucleotides targeted to various regions of HBsAg gene of human HBV effectively inhibit HBV viral gene expression in cells *in vitro*. They suggest that antisense oligonucleotides targeted to HBsAg therefore have a therapeutic potential for treating HBV infection in patients *in vivo*. See Table 1 and pages 3021-3024.

Welch et al. teach that a hairpin ribozyme targeted to HBsAg gene reduce HBV viral production and replication in HBV-infected cells *in vitro*. They suggest that anti-HBsAg ribozymes therefore have a therapeutic potential for treating HBV infections. See the entire reference.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the method of Kay et al. by targeting the surface antigen gene of HBV (HBsAg) as suggested by Stuyver et al., Goodarzi et al., and Welch et al., in order to inhibit or treat HBV viral replication and infection in cells *in vitro* or in an organism *in vivo*.

One of ordinary skill in the art would have been motivated to make such a modification in the method of Kay et al. with a reasonable expectation of success because the HBsAg gene of HBV was known to be shared among all subtypes of HBV and therefore, it was recognized as one of the highly desired target genes for nucleic acid-mediated HBV inhibition as exemplified by HBsAg antisense oligonucleotides of Goodarzi et al. and by HBsAg ribozyme of Welsh et al. Since the oligonucleotide sequence of SEQ ID NO:75 of Stuyver et al. was known to hybridize specifically with the HBsAg gene of HBV and successfully identifies as well as amplifies the HBsAg gene, and since this particular sequence was relatively well-conserved among 35 different HBV subtype genomic sequences compared to other regions of the HBsAg gene (see the boxed area in Figure 1D, which is replicated above), it would have flowed logically to one of

ordinary skill in the art to adopt the siRNA-mediated HBV inhibition method of Kay et al. and modify the method by changing the siRNA target sequence to include the well-conserved nucleotide sequence region of HBsAg in order to maximize the degree of HBV inhibition by silencing one of the most well-conserved and highly antigenic regions of the HBsAg gene as taught by Stuyver et al. Since the method of inhibiting HBV vial infection and replication via siRNA technology was known in the art prior to this application was filed, and since the instantly claimed target sequence was known to be a highly desirable target site for inhibiting HBV viral infection and replication, the claimed invention taken as a whole would have been *prima facie* obvious at the time of filing.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dana Shin whose telephone number is 571-272-8008. The examiner can normally be reached on Monday through Friday, from 8am-4:30pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Douglas Schultz can be reached on 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Dana Shin
Examiner
Art Unit 1635

/J. E. Angell/
Primary Examiner
Art Unit 1635